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THE CONTROL OF ISOMER DISTRIBUTIONS IN NITRATION REACTIONS. (U)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The direct metallation of benzene and its derivatives by mercury(II), thallium(III), lead(IV), and palladium(II) has been investigated. Mercury(II) and palladium(II) catalyze the nitration of toluene and other aromatic compounds. A novel isomer distribution is realized because the metallation reaction is the rate-controlling and product-controlling step. The nitration of toluene via thallation-nitrosode thallation produces a more random product		

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distribution in a non-catalytic reaction. The plumbylation of toluene is an unusually selective reaction. The aryllead(IV) compounds can be cleaved by a variety of reagents to form carbon-halogen, carbon-nitrogen, carbon-sulfur, and carbon-carbon bonds.

Nitronium ion carriers have also been investigated. The product distributions for the nitration of toluene using acyl carriers, e.g. $\text{CF}_3\text{CO}_2\text{-NO}_2$, $\text{CH}_3\text{CO}_2\text{-NO}_2$, $\text{C}_6\text{H}_5\text{CO}_2\text{-NO}_2$ or pyridinium carriers, e.g. $\text{XC}_5\text{H}_4\text{N-NO}_2^+$, are very similar when the reactions are carried out under comparable conditions. The O-NO_2 and N-NO_2 bonds are not broken in the product determining step.

This research has established that the nitronium ion carrier approach is not a fruitful one for the alteration of product distributions in nitration reactions. It seems doubtful that isomer distributions can be, in general, controlled by tactics of this kind. On the other hand, this research work indicates that the metal mediated electrophilic substitution reactions offer an effective approach for the control of isomer distributions. More work is needed in this area to exploit this method for catalysis and the simultaneous control of isomer distributions in a variety of substitution reactions.

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THE CONTROL OF ISOMER DISTRIBUTIONS IN NITRATION REACTIONS

FINAL REPORT

LEON M. STOCK

JUNE 10, 1980

U. S. ARMY RESEARCH OFFICE

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Table of Contents

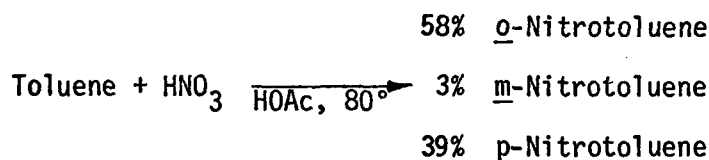
Metal Mediated Reactions1
Mercury(II).1
Thallium(III).2
Lead(IV).3
Palladium(II).5
Nitronium Ion Carriers.8
Conclusion.	11
References.	11

The Control of Isomer Distributions in Nitration Reactions

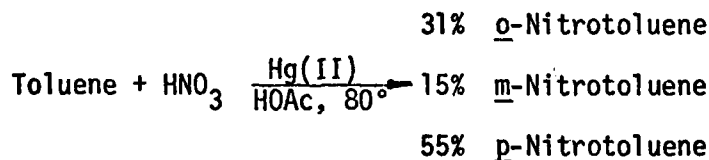
Final Report

Research on the use of metallic reagents in electrophilic substitution reactions and on metal catalyzed nitration reactions has been underway in this laboratory. The possibility that Lewis bases might serve as nitronium ion carriers has also been under study. A résumé of the research is presented in this final report. Interested readers should consult the publications or the principal investigator for more detailed information.

Mercury(II).--The original objective of the research was the discovery of methods for the selective control of isomer distributions in aromatic substitution reactions via the intervention of metallic reagents. The achievement of the control of directive effects is well illustrated by the mercury(II) acetate catalyzed nitration reaction (Stock and Wright, 1977, 1979). The isomer distribution for the uncatalyzed reaction is shown in the equation. The mercuric acetate

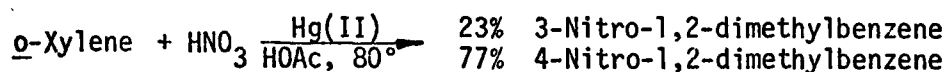


catalyzed reaction yields a very different product distribution. Study of the reaction established that the rate and product controlling reaction is mercura-

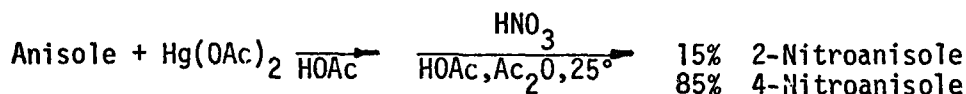
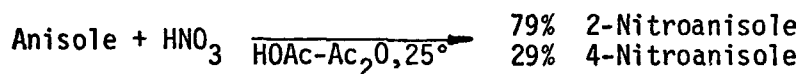


tion and that the initial mercuration product undergoes nitrosodemercuration to produce nitrosotoluenes which are rapidly oxidized to nitrotoluenes (Stock and Wright, 1977). Study of the scope of the catalytic reaction revealed that hydrocarbons of intermediate reactivity, e.g., o-xylene or t-butylbenzene, readily undergo this catalyzed nitration reaction (Stock and Wright, 1979). The cata-

lyzed nitration reaction of o-xylene is far superior to the conventional nitration procedures because the many by-products resulting from ipso substitution and side-chain oxidation reactions are completely suppressed.



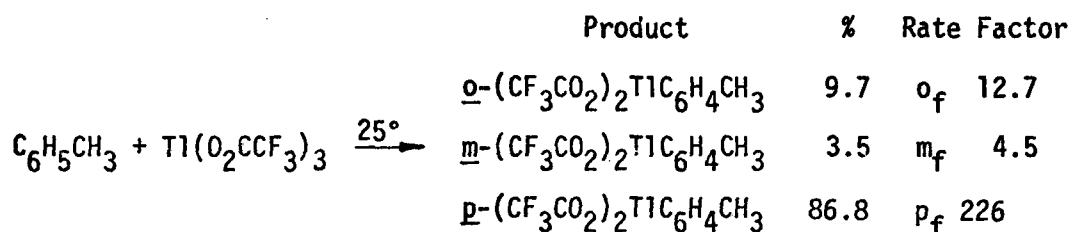
The method can also be used for the control of the product distributions in the nitration reactions of aryl ethers. Somewhat different procedures must be used because the highly reactive aromatic molecules undergo nitrosation and nitration at rates which are comparable with the rate of the mercuration reaction. We successfully produced the nitroanisoles in about 75% yield through a two-step procedure. The ortho to para ratio changed from 71:29 in the uncatalyzed reaction to 15:85 in the catalyzed reaction (Stock and Wright, 1979).



The stated objective of the development of a metal catalyzed nitration reaction was fully realized for mercury(II). The procedures developed in this research are suitable for the synthesis of a variety of nitro compounds. The approach is especially suitable when it is desirable to direct the isomer distribution toward the isomer distribution achievable in the mercuration reaction. This procedure is therefore particularly appropriate when an isomer distribution with an enriched quantity of the para isomer is desired.

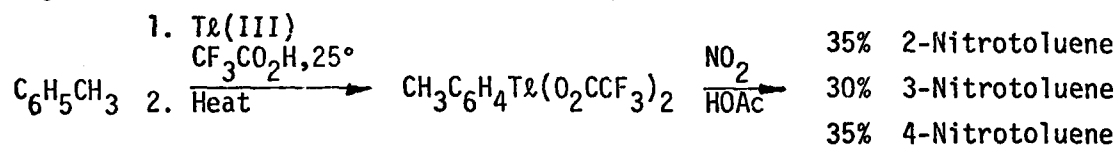
Thallium(III).--During the course of this research we also considered the use of thallium(III) as a catalyst for the nitration reaction. We determined the partial rate factors for the thallation of toluene in trifluoroacetic acid

(Kwok, Stock, and Wright, 1979). The results presented in the equation are in



good accord with the data obtained independently by Olah, Hasimoto, and Lin (1977).

We also investigated the use of thallium(III) as a catalytic agent for nitration. While this endeavor was not successful we worked out a convenient procedure for the conversion of the isomeric tolylthallium(III) compounds ^{obtained} under conditions of kinetic control to the thermodynamically stable mixture.* The procedure involves the initial reaction of toluene with thallium(III) trifluoroacetate followed by isomerization to the thermodynamically stable tolylthallium(III) compounds. These products were separated from trifluoroacetic acid and treated with nitrogen dioxide in acetic acid.

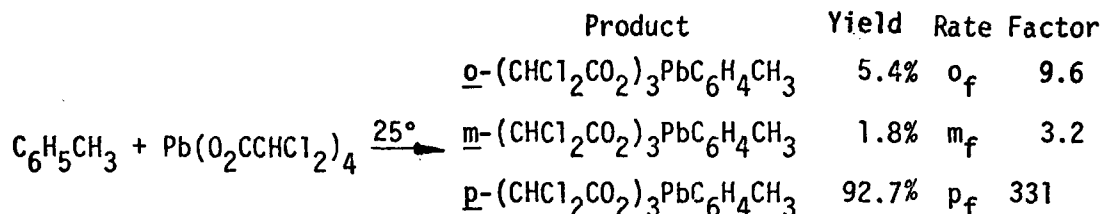


*Davis and Thomas (1975) reported that this could not be accomplished.

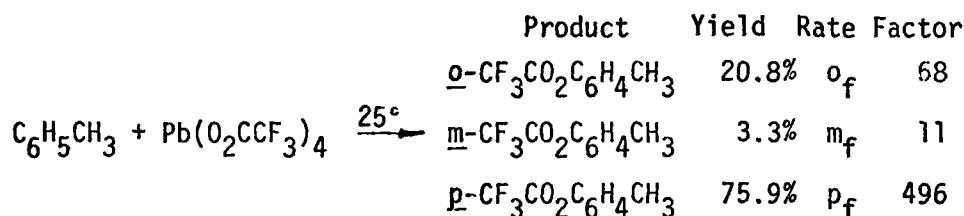
This procedure should be generally suitable for the preparation of thermodynamic product distributions and may be of special interest in research directed toward the production of novel mixtures of di and trinitrotoluenes.

Lead(IV).---We next turned attention to the use of lead(IV) compounds for aromatic substitution reactions. Reports (Bell et al., 1975; de Vos et al., 1975) concerning the successful direct metallation of aromatic compounds under mild conditions in halogenated acetic acid solvents provided a starting point for this work. In dichloroacetic acid solution, lead(IV) reacts with toluene

as shown in the equations (Stock and Wright, 1980). The reaction in trifluoroacetic acid yields the tolyltrifluoroacetates directly. A small quantity of bi-

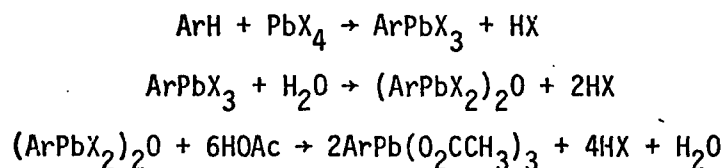


aryls are formed in a side reaction.* The products and partial rate factors for this selective reaction are presented in the next equation.



The results indicate that plumbylation is a quite selective electrophilic substitution reaction with not more than 3% meta substitution products.

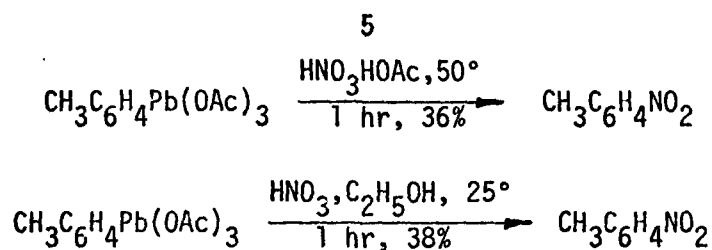
Good methods are now available for the preparation of pure aryllead compounds via plumboxane derivatives.



X = Halogenated carboxylic acid group.

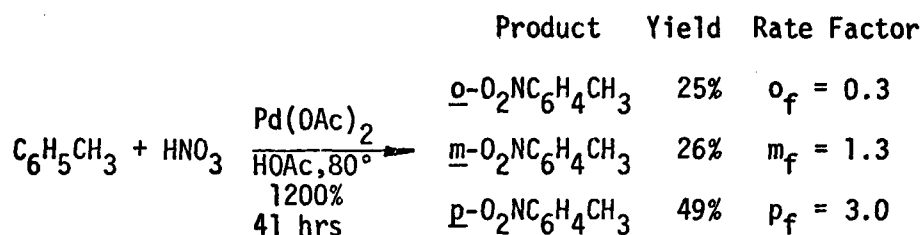
The 4-methylphenyllead(IV) derivative was reacted with several nitrodeplumbylation and nitrosodeplumbylation reagents to assess the practicality of the reaction.

* The quantity of biaryls formed in the reaction depends upon the concentration of toluene. The product distribution indicates that the arylating agent is an electrophilic reagent. Furthermore it has been established that the biaryl product distribution realized with $\text{C}_6\text{H}_5\text{N}_2^+$ in trifluoroacetic acid solution is similar to the product distribution realized with $\text{C}_6\text{H}_5\text{Pb}(\text{O}_2\text{CCF}_3)_3$ in the same solvent.

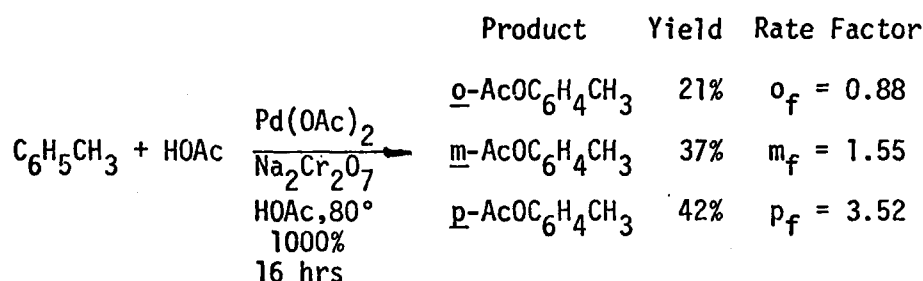


Our attempts to catalyze the conversion of toluene to nitrotoluene in the presence of lead(IV) acetates were not successful. However, the observations made in the course of the work prompted further study of the other replacement processes. It was readily established that the carbon-lead bond in the aromatic compounds was cleaved by a variety of reagents with the effective formation of carbon-hydrogen, carbon-halogen, and carbon-sulfur bonds as well as carbon-oxygen and carbon-carbon bonds. More work remains to be done but it seems clear that there is great potential for new synthetic chemistry in this area (Wright, 1979).

Palladium(II).--There are two reports in the literature concerning the use of palladium acetate as a catalyst for the nitration of aromatic compounds. In 1969, Tisue and Downs reported that palladium black catalyzed the reaction of sodium nitrite with benzene in acetic acid at 100°. In 1975, Norman, Parr, and Thomas reported that the reaction could be more effectively accomplished with nitrogen dioxide in chloroacetic acid. New work in this laboratory has confirmed that palladium acetate is an effective catalyst for the nitration reaction. Under the conditions used by the English workers numerous by-products are formed. In addition, while the reaction with nitrogen dioxide in chloroacetic acid is catalytic, the yield of product does not exceed about 300% based on palladium acetate. Study of the reaction in acetic acid, dichloroacetic acid, and trifluoroacetic acid indicated that the best results could be obtained in the acetic acid. The products were obtained in about 1200% yield using nitric acid as the reagent. Presumably further improvements could be made in development research.



A novel isomer distribution is obtained. A similar isomer distribution is obtained when toluene is catalytically oxidized under almost equivalent experimental conditions (Henry, 1974; Vorvick and Walstrum, 1978).



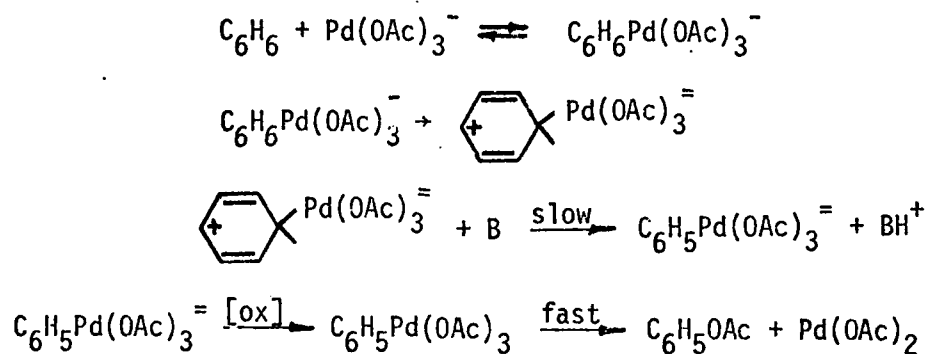
The reactivities of benzene and toluene are similar in the two reactions and the isomer distribution is quite random for oxidation and nitration. Consequently it seems reasonable to conclude that palladation is the rate determining and product determining step of the reaction and that the acetate and nitro groups are introduced into the aromatic nucleus in subsequent fast reactions.

The reactions which convert the organopalladium intermediates into the aryl acetate or into the nitro compounds are not defined. Whether the reactions occur via an electrophilic substitution reaction as appears to be the case for the mercury derivatives or via an acid-catalyzed nucleophilic substitution reaction as appears to be the case for the lead derivatives is not known.

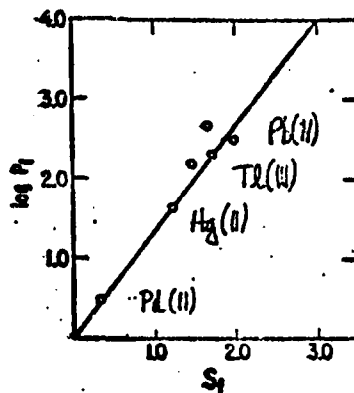
Although certain rather novel ideas have been advanced to account for the high quantity of the meta isomer formed in these reactions, the customary parallel between the inter- and the intramolecular selectivity expected for electrophilic aromatic substitution reactions is observed. Thus, the results are best accommo-

dated by a reaction mechanism involving the formation of a benzenonium ion which is converted to an arylpalladium acetate in the rate limiting step of the reaction. The characteristics of the reaction of the arylpalladium acetate have been examined indirectly. It is evident that an oxidizing agent is necessary for a successful reaction. However, the reaction rate is not dependent upon the concentration of the oxidizing agent. This fact coupled with the observations that the reaction proceeds with a primary isotope effect and that the aromatic compound does not exchange with the labeled solvent suggests that the nitration and oxidation reactions proceed through a common intermediate.

These results suggest that the reaction occurs in several steps (Vorvick and Walstrum, 1979).



Selectivity.--The selectivity of the reactions of palladium(II), mercury(II), thallium(III), and lead(IV) have been examined quantitatively under similar reaction conditions. The results clearly conform to the selectivity relationship devised for more than 100 reactions of toluene. There is a clear relationship between



the intermolecular and intramolecular selectivity of all these reagents. Curiously, palladium(II) is the least selective reaction among this group.

Nitronium Ion Carriers.--An approach for the control of isomer distributions in nitration reactions involves the use of carriers for the nitronium ion reagent. In principle, the complexed nitronium ion should exhibit quite different selectivity in its reactions with the aromatic substrates. The point is well illustrated by the well known results for chlorination. The product distributions in the reactions with toluene differ discernibly with large variations in the para to meta ratio. These variations have been widely attributed to variations in the selectivity of the chlorination reagent as a consequence of the carrier or the catalyst (de la Mare, 1976).

These results and a favorable report by Cupas and Pearson (1968) suggesting that pyridine has an influence on the nitration reaction prompted us to consider this alternative approach for the control of the product distribution. The work carried out in this laboratory complements and extends the work carried out in other laboratories. We examined the reactivity of N-nitropyridinium salts and other N-nitronium salts as well as mixed anhydrides of nitric acid with various carboxylic acids. A common solvent, acetonitrile, was employed such that solvent solute interactions remain constant throughout the course of the investigation. The results for the pyridines are summarized in Tables I and II.

The results summarized in the tables establish that the nitronium ion carrier is ineffective for the control of isomer distributions even in the case where the steric requirements of the substrate are large.

Table I. Product Distributions in the Nitration of Toluene with Nitronium Salts in the Presence of Pyridines in Acetonitrile.^a

Nitronium Ion Carrier Pyridine Substituent	Product Distribution			Notes
	o-	m-	p-	
None	60.0	3.4	36.6	Heterogeneous, low yield
2-Methyl	63.7	3.6	32.7	
2-Fluoro	65.0	3.4	31.6	
2-Chloro	63.1	3.9	33.0	Heterogeneous, low yield
2-Bromo	63.2	3.7	33.1	Low Yield
2-Methoxy	62.5	3.6	33.9	
3-Chloro	64.3	3.4	32.3	
3-Bromo	62.5	3.5	34.0	Low Yield
2,4-Dimethyl	63.3	3.6	33.1	
2,4,6-Trimethyl	63	3	34	
2-Methyl-4-nitro	66.4	4.3	29.3	

^aGreenberg, 1979.

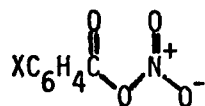
Table II. Product Distributions in the Nitration of *t*-Butylbenzene with Nitronium Salts in the Presence of Pyridines in Acetonitrile.^a

Reaction	Product Distribution		
	o-	m-	p-
Control Experiment	11	15	74
2-Methylpyridine	11	14	75
2-Fluoropyridine	11	14	75

^aGreenberg, 1979.

We also studied the carboxylate carriers. Olah and his students, 1978, noted that the mixed anhydride carriers formed from substituted benzoic acids and nitric

acid react with toluene and benzene in a similar fashion. Kurz and his group, 1973,



made a similar finding. The X substituent does not alter either the intermolecular reactivity as judged from the toluene to benzene rate ratio or the intramolecular selectivity as judged from the isomer distribution. We reasoned that the X substituent is remote from the reaction site and may therefore have only a negligible influence on the reaction. Accordingly, we examined the reactions of the mixed anhydrides of nitric acid with acetic acid and trifluoroacetic acid under the same conditions. The work with benzoic acid was repeated to secure the analytical methods. The product distribution for the reactions carried out in acetonitrile are summarized in Table III.

Table III. Product Distributions for the Nitration of Toluene by RCO_2NO_2 Reagents in Acetonitrile.^a

Reagent, conditions	Product Distribution		
	o-	m-	p-
$\text{C}_6\text{H}_5\text{COCl}, \text{AgNO}_3, \text{CH}_3\text{CN}, 0^\circ$	63.1	3.4	33.5
$(\text{CH}_3\text{CO})_2\text{O}, \text{HNO}_3, \text{CH}_3\text{CN}, 0^\circ$	64.8	3.1	32.1
$(\text{CF}_3\text{CO})_2\text{O}, \text{HNO}_3, \text{CH}_3\text{CN}, 0^\circ$	65.3	3.1	31.6

^aBookbinder and Greenberg, 1979.

The information presented in Table III is in complete accord with the information obtained by Kurz et al., 1973. The same isomer distributions are obtained independent of the structure of the carboxylate group. Indeed, the same isomer distributions are obtained in the case of the pyridines as in the case of the carboxylic

acids. All these results point very strongly to an interpretation based on the idea that the product determining step occurs after the O-NO₂ and N-NO₂ bonds are broken and that the factors which govern the product determining steps are not in the least influenced by the presence of the carrier.

It is difficult to envision a nitronium ion carrier which would be effective for the control of the isomer distribution. Consequently, we abandoned efforts to achieve the control of the product distribution by this tactic.

Conclusion

Two principal conclusions emerge from this research. First, as just mentioned, the nitronium ion carrier approach for the control of isomer distributions is not fruitful. Second, there are many positive indications that homogeneous catalytic reactions using metallic reagents will have a broad scope and will provide useful methods for the control of isomer distributions in aromatic substitution reactions. More work is needed on this aspect of the problem.

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